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 NEWS  1          Web Page URLs for STN Seminar Schedule - N. America
 NEWS  2          "Ask CAS" for self-help around the clock
 NEWS  3  FEB 27  New STN AnaVist pricing effective March 1, 2006
 NEWS  4  APR 04  STN AnaVist $500 visualization usage credit offered
 NEWS  5  MAY 10  CA/CAplus enhanced with 1900-1906 U.S. patent records
 NEWS  6  MAY 11  KOREAPAT updates resume
 NEWS  7  MAY 19  Derwent World Patents Index to be reloaded and enhanced
 NEWS  8  MAY 30  IPC 8 Rolled-up Core codes added to CA/CAplus and
                  USPATFULL/USPAT2
 NEWS  9  MAY 30  The F-Term thesaurus is now available in CA/CAplus
 NEWS 10  JUN 02  The first reclassification of IPC codes now complete in
                  INPADOC
 NEWS 11  JUN 26  TULSA/TULSA2 reloaded and enhanced with new search and
                  and display fields

 NEWS EXPRESS     FEBRUARY 15 CURRENT VERSION FOR WINDOWS IS V8.01a,
                  CURRENT MACINTOSH VERSION IS V6.0c(ENG) AND V6.0Jc(JP),
                  AND CURRENT DISCOVER FILE IS DATED 26 JUNE 2006.
                  V8.0 AND V8.01 USERS CAN OBTAIN THE UPGRADE TO V8.01a AT
                  http://download.cas.org/express/v8.0-Discover/

 NEWS HOURS    STN Operating Hours Plus Help Desk Availability
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* * * * * * * * * * * * * * * STN Columbus * * * * * * * * * * * * * * * *

FILE 'HOME' ENTERED AT 08:51:58 ON 27 JUN 2006

=> file reg
COST IN U.S. DOLLARS                                  SINCE FILE     TOTAL
                                                           ENTRY   SESSION
FULL ESTIMATED COST                                         0.21      0.21

FILE 'REGISTRY' ENTERED AT 08:52:10 ON 27 JUN 2006
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.
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Property values tagged with IC are from the ZIC/VINITI data file
provided by InfoChem.

STRUCTURE FILE UPDATES:   26 JUN 2006  HIGHEST RN 889573-50-6
DICTIONARY FILE UPDATES:  26 JUN 2006  HIGHEST RN 889573-50-6

New CAS Information Use Policies, enter HELP USAGETERMS for details.

TSCA INFORMATION NOW CURRENT THROUGH January 6, 2006

  Please note that search-term pricing does apply when
  conducting SmartSELECT searches.

*******************************************************************
*                                                                 *
* The CA roles and document type information have been removed from *
* the IDE default display format and the ED field has been added,    *
* effective March 20, 2005.  A new display format, IDERL, is now     *
* available and contains the CA role and document type information. *
*                                                                 *
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Structure search iteration limits have been increased.  See HELP SLIMITS
for details.

REGISTRY includes numerically searchable data for experimental and
predicted properties as well as tags indicating availability of
experimental property data in the original document.  For information
on property searching in REGISTRY, refer to:

http://www.cas.org/ONLINE/UG/regprops.html

=> s KAKAGAGSATLSMAYAGARFVFSLVDAMNGKEGVVECSFVKSQETECTYFSTPLLLGKKGIEKNLGIGKVSS/SQEP
             2 KAKAGAGSATLSMAYAGARFVFSLVDAMNGKEGVVECSFVKSQETECTYFSTPLLLGKKGIEKN
               LGIGKVSS/SQEP
         28992 SQL=72
L1           2 KAKAGAGSATLSMAYAGARFVFSLVDAMNGKEGVVECSFVKSQETECTYFSTPLLLGKKGIEKN
               LGIGKVSS/SQEP
                 (KAKAGAGSATLSMAYAGARFVFSLVDAMNGKEGVVECSFVKSQETECTYFSTPLLLGKKGI
                 EKNLGIGKVSS/SQEP AND SQL=72)

=> s KAKAGAGSATLSMAYAGARFVFSLVDAMNGKEGVVECSFVKSQETECTYFSTPLLLGKKGIEKNLGIGKVSS/SQSP
L2          23 KAKAGAGSATLSMAYAGARFVFSLVDAMNGKEGVVECSFVKSQETECTYFSTPLLLGKKGIEKN
               LGIGKVSS/SQSP

=> file caplus
COST IN U.S. DOLLARS                              SINCE FILE     TOTAL
                                                       ENTRY   SESSION
FULL ESTIMATED COST                                    36.38     36.59

FILE 'CAPLUS' ENTERED AT 08:53:05 ON 27 JUN 2006
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.
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FILE COVERS 1907 - 27 Jun 2006  VOL 145 ISS 1
FILE LAST UPDATED: 26 Jun 2006  (20060626/ED)

Effective October 17, 2005, revised CAS Information Use Policies apply.
They are available for your review at:

http://www.cas.org/infopolicy.html

=> s l1 or l2
              2 L1
             18 L2
L3           18 L1 OR L2

=> s l3 not py>2002
        4004323 PY>2002
L4            2 L3 NOT PY>2002

=> d ibib 1-2

L4   ANSWER 1 OF 2  CAPLUS  COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER:         2003:18945  CAPLUS
DOCUMENT NUMBER:          138:67676
TITLE:                    Generation and initial analysis of more than 15,000
                          full-length human and mouse cDNA sequences
AUTHOR(S):                Strausberg, Robert L.; Feingold, Elise A.; Grouse,
                          Lynette H.; Derge, Jeffery G.; Klausner, Richard D.;
                          Collins, Francis S.; Wagner, Lukas; Shenmen, Carolyn
                          M.; Schuler, Gregory D.; Altschul, Stephen F.;
                          Zeeberg, Barry; Buetow, Kenneth H.; Schaefer, Carl F.;
                          Bhat, Narayan K.; Hopkins, Ralph F.; Jordan, Heather;
                          Moore, Troy; Max, Steve I.; Wang, Jun; Hsieh,
                          Florence; Diatchenko, Luda; Marusina, Kate; Farmer,
                          Andrew A.; Rubin, Gerald M.; Hong, Ling; Stapleton,
                          Mark; Soares, M. Bento; Bonaldo, Maria F.; Casavant,
                          Tom L.; Scheetz, Todd E.; Brownstein, Michael J.;
                          Usdin, Ted B.; Toshiyuki, Shiraki; Carninci, Piero;
                          Prange, Christa; Raha, Sam S.; Loquellano, Naomi A.;
                          Peters, Garrick J.; Abramson, Rick D.; Mullahy, Sara
                          J.; Bosak, Stephanie A.; McEwan, Paul J.; McKernan,
                          Kevin J.; Malek, Joel A.; Gunaratne, Preethi H.;
                          Richards, Stephen; Worley, Kim C.; Hale, Sarah;
                          Garcia, Angela M.; Gay, Laura J.; Hulyk, Stephen W.;
                          Villalon, Debbie K.; Muzny, Donna M.; Sodergren, Erica
                          J.; Lu, Xiuhua; Gibbs, Richard A.; Fahey, Jessica;
                          Helton, Erin; Ketteman, Mark; Madan, Anuradha;
                          Rodrigues, Stephanie; Sanchez, Amy; Whiting, Michelle;
                          Madan, Anup; Young, Alice C.; Shevchenko, Yuriy;
                          Bouffard, Gerard G.; Blakesley, Robert W.; Touchman,
                          Jeffrey W.; Green, Eric D.; Dickson, Mark C.;
                          Rodriguez, Alex C.; Grimwood, Jane; Schmutz, Jeremy;
                          Myers, Richard M.; Butterfield, Yaron S. N.;
                          Krzywinski, Martin I.; Skalska, Ursula; Smailus, Duane
                          E.; Schnerch, Angelique; Schein, Jacqueline E.; Jones,
                          Steven J. M.; Marra, Marco A.
CORPORATE SOURCE:         National Cancer Institute, NIH, Bethesda, MD,
                          20892-2580, USA
SOURCE:                   Proceedings of the National Academy of Sciences of the
                          United States of America (2002), 99(26), 16899-16903
                          CODEN: PNASA6; ISSN: 0027-8424
PUBLISHER:                National Academy of Sciences
DOCUMENT TYPE:            Journal
LANGUAGE:                 English
REFERENCE COUNT:          18    THERE ARE 18 CITED REFERENCES AVAILABLE FOR THIS
                                RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT
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L4   ANSWER 2 OF 2  CAPLUS  COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER:         2001:592185  CAPLUS
DOCUMENT NUMBER:          135:177271
TITLE:                    Cloning, sequencing and therapeutic use of human
                          mitochondrial malate dehydrogenase
INVENTOR(S):              Bandman, Olga; Corley, Neil C.; Shah, Purvi
PATENT ASSIGNEE(S):       Incyte Genomics, Inc., USA
SOURCE:                   U.S., 34 pp.
                          CODEN: USXXAM
DOCUMENT TYPE:            Patent
LANGUAGE:                 English
FAMILY ACC. NUM. COUNT:   1
PATENT INFORMATION:

     PATENT NO.          KIND    DATE          APPLICATION NO.        DATE
     ---------------     ----    --------      --------------------   --------
     US 6274138           B1     20010814      US 1997-922957         19970903
     US 2002086006        A1     20020704      US 2001-915694         20010725
PRIORITY APPLN. INFO.:                         US 1997-922957      A3 19970903
REFERENCE COUNT:          15     THERE ARE 15 CITED REFERENCES AVAILABLE FOR THIS
                                 RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT


=> d his

     (FILE 'HOME' ENTERED AT 08:51:58 ON 27 JUN 2006)

     FILE 'REGISTRY' ENTERED AT 08:52:10 ON 27 JUN 2006
L1            2 S KAKAGAGSATLSMAYAGARFVFSLVDAMNGKEGVVECSFVKSQETECTYFSTPLLLGKKGI
L2           23 S KAKAGAGSATLSMAYAGARFVFSLVDAMNGKEGVVECSFVKSQETECTYFSTPLLLGKKGI

     FILE 'CAPLUS' ENTERED AT 08:53:05 ON 27 JUN 2006
L3           18 S L1 OR L2
L4            2 S L3 NOT PY>2002

=> s l1
L5            2 L1

=> d ibib 1-2

L5   ANSWER 1 OF 2  CAPLUS  COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER:         2004:681680  CAPLUS
DOCUMENT NUMBER:          141:200162
TITLE:                    Mitochondrial malate dehydrogenase DNA fragmentation
                          activator fragment and related conjugated proteins and
                          antibodies for cancer therapy
INVENTOR(S):              Wright, Susan C.; Larrick, James W.; Nock, Steffen R.;
                          Wilson, David S.
PATENT ASSIGNEE(S):       Palo Alto Institute of Molecular Medicine, USA
SOURCE:                   PCT Int. Appl., 225 pp.
                          CODEN: PIXXD2
DOCUMENT TYPE:            Patent
LANGUAGE:                 English
FAMILY ACC. NUM. COUNT:   1
PATENT INFORMATION:

     PATENT NO.          KIND    DATE          APPLICATION NO.        DATE
     ---------------     ----    --------      --------------------   --------
     WO 2004070012        A2     20040819      WO 2004-US2974         20040202
     WO 2004070012        A3     20060330
         W:  AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH,
             CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD,
             GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC,
             LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI,
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              NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY,
              TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
          RW: BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE,
              BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU,
              MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN,
              GQ, GW, ML, MR, NE, SN, TD, TG, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
     AU 2004209644          A1     20040819   AU 2004-209644          20040202
     CA 2514841             AA     20040819   CA 2004-2514841         20040202
     US 2004191843          A1     20040930   US 2004-770668          20040202
     EP 1590440             A2     20051102   EP 2004-707424          20040202
         R:  AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,
             IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK
PRIORITY APPLN. INFO.:                            US 2003-444191P     P  20030203
                                                  US 2003-460855P     P  20030408
                                                  US 2004-770668      A  20040202
                                                  WO 2004-US2974      W  20040202

L5   ANSWER 2 OF 2  CAPLUS  COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER:         2004:681539  CAPLUS
DOCUMENT NUMBER:          141:212819
TITLE:                    Compounds useful in coating stents to prevent and
                          treat stenosis and restenosis
INVENTOR(S):              Wang, Yuqiang; Larrick, James W.; Wright, Susan C.
PATENT ASSIGNEE(S):       Medlogics Device Corporation, USA
SOURCE:                   PCT Int. Appl., 63 pp.
                          CODEN: PIXXD2
DOCUMENT TYPE:            Patent
LANGUAGE:                 English
FAMILY ACC. NUM. COUNT:   1
PATENT INFORMATION:

     PATENT NO.          KIND    DATE        APPLICATION NO.         DATE
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     WO 2004069201        A2     20040819    WO 2004-US3143          20040203
     WO 2004069201        A3     20050519
         W:  AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH,
             CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD,
             GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC,
             LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI
         RW: BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE,
             BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU,
             MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN,
             GQ, GW, ML, MR, NE, SN, TD, TG
PRIORITY APPLN. INFO.:                           US 2003-444391P     P  20030203
OTHER SOURCE(S):          MARPAT 141:212819

=> d abs 2

L5   ANSWER 2 OF 2  CAPLUS  COPYRIGHT 2006 ACS on STN
AB   At least one bioactive agent is locally delivered to a location where a
     stent is implanted within a lumen in a patient's body.  The bioactive
     agent includes DNA minor groove binder (such as CC-1065 or Duocarmycin);
     apocynin; RGD peptide (such as RGDfV); stilbene compound (such as
     resveratrol); camptothecin; des-aspartate angiotensin I; or ADF; or an
     analog or derivative thereof; or a combination or blend thereof with at least
     one other bioactive agent.  The bioactive agent is generally locally
     delivered, such as by elution from the stent.  The compds. and methods are
     of particular benefit for treating or preventing atherosclerosis,
     stenosis, restenosis, smooth muscle cell proliferation, occlusive disease,
     or other abnormal lumenal cellular proliferation condition.

=> s l2
L6          18 L2
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=> s l6 not l5
L7          16 L6 NOT L5

=> s l7 not py>2003
       2937472 PY>2003
L8           3 L7 NOT PY>2003

=> d ibib 1-3

L8   ANSWER 1 OF 3  CAPLUS  COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER:         2003:942764  CAPLUS
DOCUMENT NUMBER:          140:3792
TITLE:                    Genes expressed in atherosclerotic tissue and their
                          use in diagnosis and pharmacogenetics
INVENTOR(S):              Nevins, Joseph; West, Mike; Goldschmidt, Pascal
PATENT ASSIGNEE(S):       Duke University, USA
SOURCE:                   PCT Int. Appl., 408 pp.
                          CODEN: PIXXD2
DOCUMENT TYPE:            Patent
LANGUAGE:                 English
FAMILY ACC. NUM. COUNT:   3
PATENT INFORMATION:

     PATENT NO.          KIND   DATE       APPLICATION NO.         DATE
     ---------------     ----   --------   --------------------    --------
     WO 2003091391        A2    20031106   WO 2002-XA38221         20021112
         W:  AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ,
             DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IS, JP,
             KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN,
             MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM,
             TR, TT, UA, UG, UZ, VN, YU, ZA, ZW
        RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG,
             CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL,
             PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR,
             NE, SN, TD, TG
     WO 2003091391        A2    20031106   WO 2002-US38221         20021112
         W:  AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ,
             DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IS, JP,
             KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN,
             MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM,
             TR, TT, UA, UG, UZ, VN, YU, ZA, ZW
        RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY,
             KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES,
             FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF,
             CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG
PRIORITY APPLN. INFO.:                     US 2002-374547P     P  20020423
                                           US 2002-420784P     P  20021024
                                           US 2002-421043P     P  20021025
                                           US 2002-424680P     P  20021108
                                           WO 2002-US38221     A  20021112

L8   ANSWER 2 OF 3  CAPLUS  COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER:         2003:18945  CAPLUS
DOCUMENT NUMBER:          138:67676
TITLE:                    Generation and initial analysis of more than 15,000
                          full-length human and mouse cDNA sequences
AUTHOR(S):                Strausberg, Robert L.; Feingold, Elise A.; Grouse,
                          Lynette H.; Derge, Jeffery G.; Klausner, Richard D.;
                          Collins, Francis S.; Wagner, Lukas; Shenmen, Carolyn
                          M.; Schuler, Gregory D.; Altschul, Stephen F.;
                          Zeeberg, Barry; Buetow, Kenneth H.; Schaefer, Carl F.;
                          Bhat, Narayan K.; Hopkins, Ralph F.; Jordan, Heather;
                          Moore, Troy; Max, Steve I.; Wang, Jun; Hsieh,
                          Florence; Diatchenko, Luda; Marusina, Kate; Farmer,
```

Andrew A.; Rubin, Gerald M.; Hong, Ling; Stapleton, Mark; Soares, M. Bento; Bonaldo, Maria F.; Casavant, Tom L.; Scheetz, Todd E.; Brownstein, Michael J.; Usdin, Ted B.; Toshiyuki, Shiraki; Carninci, Piero; Prange, Christa; Raha, Sam S.; Loquellano, Naomi A.; Peters, Garrick J.; Abramson, Rick D.; Mullahy, Sara J.; Bosak, Stephanie A.; McEwan, Paul J.; McKernan, Kevin J.; Malek, Joel A.; Gunaratne, Preethi H.; Richards, Stephen; Worley, Kim C.; Hale, Sarah; Garcia, Angela M.; Gay, Laura J.; Hulyk, Stephen W.; Villalon, Debbie K.; Muzny, Donna M.; Sodergren, Erica J.; Lu, Xiuhua; Gibbs, Richard A.; Fahey, Jessica; Helton, Erin; Ketteman, Mark; Madan, Anuradha; Rodrigues, Stephanie; Sanchez, Amy; Whiting, Michelle; Madan, Anup; Young, Alice C.; Shevchenko, Yuriy; Bouffard, Gerard G.; Blakesley, Robert W.; Touchman, Jeffrey W.; Green, Eric D.; Dickson, Mark C.; Rodriguez, Alex C.; Grimwood, Jane; Schmutz, Jeremy; Myers, Richard M.; Butterfield, Yaron S. N.; Krzywinski, Martin I.; Skalska, Ursula; Smailus, Duane E.; Schnerch, Angelique; Schein, Jacqueline E.; Jones, Steven J. M.; Marra, Marco A.

```
CORPORATE SOURCE:         National Cancer Institute, NIH, Bethesda, MD,
                          20892-2580, USA
SOURCE:                   Proceedings of the National Academy of Sciences of the
                          United States of America (2002), 99(26), 16899-16903
                          CODEN: PNASA6; ISSN: 0027-8424
PUBLISHER:                National Academy of Sciences
DOCUMENT TYPE:            Journal
LANGUAGE:                 English
REFERENCE COUNT:          18    THERE ARE 18 CITED REFERENCES AVAILABLE FOR THIS
                                RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8   ANSWER 3 OF 3  CAPLUS  COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER:         2001:592185  CAPLUS
DOCUMENT NUMBER:          135:177271
TITLE:                    Cloning, sequencing and therapeutic use of human
                          mitochondrial malate dehydrogenase
INVENTOR(S):              Bandman, Olga; Corley, Neil C.; Shah, Purvi
PATENT ASSIGNEE(S):       Incyte Genomics, Inc., USA
SOURCE:                   U.S., 34 pp.
                          CODEN: USXXAM
DOCUMENT TYPE:            Patent
LANGUAGE:                 English
FAMILY ACC. NUM. COUNT:   1
PATENT INFORMATION:

     PATENT NO.          KIND   DATE        APPLICATION NO.        DATE
     ---------------     ----   --------    --------------------   --------
     US 6274138           B1    20010814    US 1997-922957         19970903
     US 2002086006        A1    20020704    US 2001-915694         20010725
PRIORITY APPLN. INFO.:                      US 1997-922957      A3 19970903
REFERENCE COUNT:          15    THERE ARE 15 CITED REFERENCES AVAILABLE FOR THIS
                                RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT


=> d kwic 1

L8   ANSWER 1 OF 3  CAPLUS  COPYRIGHT 2006 ACS on STN
IT   480917-91-7   480917-95-1   480919-09-3   480919-29-7, CAGF28 (human)
     480919-95-7, Brachyury (human gene TBX1)   480919-98-0, Cbf5p (human cell
     line HeLa gene CBF5)   480919-99-1   480920-09-0, GenBank AAB94761
     480920-38-5, GenBank AAB96655   480920-71-6, Mad4 (human gene Mad4)
     480921-77-5, Complement component C2 (human gene C2)   480922-00-7,
     GenBank AAB99730   480922-06-3   480922-10-9, BC-2 protein (human)
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480922-11-0, Cyclophilin-33B (human gene CYP-33) 480922-49-4, Mucin (human gene MUC3) 480924-07-0 480924-12-7 480924-20-7, Transcription factor LZIP (human) 480924-63-8 480924-67-2 480924-69-4, GenBank AAC05601 480924-79-6, SSX4 (human gene SSX4) 480924-98-9 480926-14-5 480926-28-1 480926-38-3 480926-40-7 480926-41-8 480926-42-9 480926-43-0 480927-06-8 480927-23-9 480928-15-2, GenBank AAC15791 480928-16-3 480929-54-2 480929-55-3 480929-66-6, Sorting nexin 2 (human gene SNX2) 480929-83-7 480929-92-8 480931-06-4 480931-07-5 480931-08-6 480931-09-7 480931-79-1 480932-16-9 480932-18-1 480932-19-2 480932-69-2, GenBank AAC26109 480933-21-9 480933-35-5 480933-36-6 480933-45-7, PLE21 protein (human gene ple21) 480933-46-8 480933-64-0, GenBank AAC28644 480934-15-4, Nucleoplasmin-3 (human gene NPM3) 480934-16-5, Lysophospholipase (human gene LPL1) 480934-44-9, Protein (human gene JH8) 480934-77-8, ATPase (human) 480934-93-8, GenBank AAC33132 480935-42-0, GenBank AAC34245 480935-86-2 480935-99-7, DNA repair exonuclease (human gene REC1) 480936-36-5 480936-86-5, Cullin 1 (human cell line HeLa) 480936-95-6, Molecular chaperone DnaJ (human) 480937-06-2, Protein (human gene NAP) 480937-27-7 480937-28-8 480937-37-9, Phosphomevalonate kinase (human) 480937-40-4 480938-12-3 480938-75-8, Kallistatin (human gene PI4) 480938-96-3 480938-99-6 480939-09-1, GenBank AAC41749 480939-14-8 480940-77-0, GenBank AAC41930 480940-78-1, GenBank AAC41931 480940-88-3 480941-34-2 480941-37-5 480941-39-7 480941-43-3 480941-52-4, Trio isoform (human) 480941-62-6 480941-63-7, P47 LBC oncogene (human clone 9a2) 480941-65-9 480942-01-6, SLP-76 (human) 480942-04-9 480942-30-1 480942-66-3 480942-70-9 480943-40-6 480943-41-7 480943-46-2 480943-51-9, Protein RGP4 (human) 480943-57-5 480943-68-8 480943-84-8 480944-02-3, Protein B (human cell line HT-1080) 480944-09-0, Metaxin (human gene MTX) 480944-41-0, Hs-CUL-1 (human gene Hs-cul-1) 480944-46-5, BA46 (human) 480944-70-5 480944-71-6 480945-09-3 480945-16-2 480945-17-3, DNA polymerase gamma (human) 480945-22-0, STAM (human) 480945-23-1, LIM protein (human gene LPP) 480946-18-7, FUSE binding protein 3 (human gene FBP3) 480946-29-0, GenBank AAC50955 480946-82-5 480947-84-0 480948-05-8, C2H2-150 (human) 480948-26-3, Uncoupling protein 3, UCP3S (human) 480948-28-5, GenBank AAC51360 480948-30-9, Phosphomannomutase (human gene PMM2) 480950-82-1, Zinc finger protein (human clone PRD51) 480951-45-9, Dead box, Y isoform (human gene DBY) 480951-46-0 480952-58-7 480953-12-6, G-protein coupled receptor RE2 (human) 480953-60-4, Protein UP50 (human urine) 480953-61-5, GenBank AAC62108 480953-69-3, GenBank AAC62428 480953-76-2 480953-89-7 480954-43-6 480954-51-6 480954-63-0, Gamma2-adaptin (human gene G2AD) 480956-14-7, GenBank AAC70911 480956-29-4 480956-30-7, GenBank AAC72105 480956-35-2 480958-09-6, Protein (human clone 559 125-amino acid) 480958-16-5, Protein (human clone 638 198-amino acid) 480958-17-6, GenBank AAC72956 480958-22-3, GenBank AAC72961 480958-31-4 480958-60-9, GenBank AAC79844 480959-13-5 481118-85-8 481122-86-5, AML1c protein (human gene AML1) 481122-88-7, AML1b protein (human gene AML1) 481123-11-9, VAMP5 (human) 481123-58-4 481123-89-1 481125-18-2 481125-24-0, GenBank AAD00702 481125-83-1, GenBank AAD01614 481126-46-9 481126-50-5, GenBank AAD02203 481126-60-7 481126-75-4, GenBank AAD03161 481126-84-5, AP-3 complex sigma3A subunit (human) 481127-04-2 481128-89-6, GenBank AAA66020 481128-90-9 481129-26-4, GenBank BAA31588 481129-29-7 481129-30-0 481129-37-7 481129-39-9 481129-47-9 481129-53-7 481129-54-8 481129-60-6, GenBank BAA34787 481130-03-4 481131-07-1, Protein (human gene HRIHFB2157) 481131-19-5, Protein MD-1 (human) 481131-62-8 481131-82-2 481132-35-8 481132-38-1 481132-48-3 481132-99-4 481133-00-0, Fln29 (human gene fln29) 481133-01-1, GenBank BAA78640 481133-20-4, DEPP (human gene DEPP) 481133-61-3 481133-62-4 481133-70-4 481134-93-4 481134-94-5 481134-96-7 481135-07-3 481135-94-8 481136-83-8 481137-03-5, GenBank BAA06626 481137-13-7 481137-22-8 481137-23-9 481137-34-2, L-histidine decarboxylase (human) 481137-54-6 481137-57-9 481138-12-9 481138-14-1 481138-46-9 481138-47-0 481138-55-0 481138-69-6 481139-37-1 481139-85-9,

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GenBank BAA07508   481140-37-8   481140-39-0, GenBank AAA70417
481140-83-4   481140-89-0, GenBank BAA05124   481140-98-1, 5'-Nucleotidase
(human)   481140-99-2   481141-09-7   481141-11-1   481141-13-3
481141-23-5   481141-28-0   481141-29-1   481141-52-0   481142-07-8,
PK-120 precursor (human)   481143-01-5, Sky (human cell line HepG2 gene
sky)   481143-06-0   481143-08-2   481143-10-6   481143-14-0   481143-35-5
481143-50-4   481143-52-6   481143-57-1   481143-61-7   481143-87-7, Human
rab GDI (human)   481144-86-9, Carbamyl phosphate synthetase I (human)
481144-91-6   481144-97-2, LIMK-2 (human clone limk-2)   481145-06-6,
Protein (human 349-amino acid)   481145-07-7   481145-28-2   481145-31-7,
Protein (human 384-amino acid)
RL: BSU (Biological study, unclassified); PRP (Properties); BIOL
(Biological study)
   (amino acid sequence; genes expressed in atherosclerotic tissue and
   their use in diagnosis and pharmacogenetics)


=> file pctfull
COST IN U.S. DOLLARS                              SINCE FILE      TOTAL
                                                       ENTRY    SESSION
FULL ESTIMATED COST                                    19.79      56.38

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)        SINCE FILE      TOTAL
                                                       ENTRY    SESSION
CA SUBSCRIBER PRICE                                    -0.75      -0.75

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FILE LAST UPDATED:          27 JUN 2006      <20060627/UP>
MOST RECENT UPDATE WEEK:       200625         <200625/EW>
FILE COVERS 1978 TO DATE

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    SEE
    http://www.stn-international.de/stndatabases/details/ipc-reform.html >>>

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    (last updated April 10, 2006) <<<

>>> NEW PRICES IN PCTFULL AS OF 01 JULY 2006. FOR DETAILS,
    PLEASE SEE HELP COST <<<

=> s (mitochondrial malate) or MDH
         10031 MITOCHONDRIAL
             1 MITOCHONDRIALS
         10031 MITOCHONDRIAL
                 (MITOCHONDRIAL OR MITOCHONDRIALS)
          6890 MALATE
           368 MALATES
          7208 MALATE
                 (MALATE OR MALATES)
            25 MITOCHONDRIAL MALATE
                 (MITOCHONDRIAL(W)MALATE)
           789 MDH
             9 MDHS
           794 MDH
                 (MDH OR MDHS)
L9         816 (MITOCHONDRIAL MALATE) OR MDH

=> s conjugat? or link?
         76223 CONJUGAT?
        303388 LINK?
```

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L10      322330 CONJUGAT? OR LINK?

=> s l9 and l10
L11         713 L9 AND L10

=> s cancer? or tumor? or neoplas?
          79320 CANCER?
          66217 TUMOR?
          23005 NEOPLAS?
L12       98755 CANCER? OR TUMOR? OR NEOPLAS?

=> s l11 and l12
L13         548 L11 AND L12

=> s antibod?
L14       88922 ANTIBOD?

=> s l13 and l14
L15         523 L13 AND L14

=> s l15 not py>2002
         414028 PY>2002
L16         259 L15 NOT PY>2002

=> s l9/clm
            931 MITOCHONDRIAL/CLM
            695 MALATE/CLM
              2 MITOCHONDRIAL MALATE/CLM
                  ((MITOCHONDRIAL(W)MALATE)/CLM)
             98 MDH/CLM
L17         100 ((MITOCHONDRIAL MALATE/CLM) OR MDH/CLM)

=> s k8/ab
L18          10 K8/AB

=> s l9/ab
            331 MITOCHONDRIAL/AB
             59 MALATE/AB
              1 MALATES/AB
             60 MALATE/AB
                  ((MALATE OR MALATES)/AB)
              0 MITOCHONDRIAL MALATE/AB
                  ((MITOCHONDRIAL(W)MALATE)/AB)
              8 MDH/AB
L19           8 ((MITOCHONDRIAL MALATE/AB) OR MDH/AB)

=> s l19 or l17
L20         101 L19 OR L17

=> s l20 and l16
L21           6 L20 AND L16

=> d ibib 1-21

L21    ANSWER 1 OF 6      PCTFULL   COPYRIGHT 2006 Univentio on STN
ACCESSION NUMBER:        2001057277 PCTFULL  ED 20020827
TITLE (ENGLISH):         HUMAN GENOME-DERIVED SINGLE EXON NUCLEIC ACID PROBES
                         USEFUL FOR ANALYSIS OF GENE EXPRESSION IN HUMAN FETAL
                         LIVER
TITLE (FRENCH):          SONDES D'ACIDE NUCLEIQUE A UN SEUL EXON DERIVEES DU
                         GENOME HUMAIN UTILES POUR ANALYSER L'EXPRESSION GENIQUE
                         DANS LE FOIE FOETAL HUMAIN
INVENTOR(S):             PENN, Sharron, G.;
                         HANZEL, David, K.;
                         CHEN, Wensheng;
```

	RANK, David, R.
PATENT ASSIGNEE(S):	MOLECULAR DYNAMICS, INC.;
	PENN, Sharron, G.;
	HANZEL, David, K.;
	CHEN, Wensheng;
	RANK, David, R.
DOCUMENT TYPE:	Patent
PATENT INFORMATION:	

NUMBER	KIND	DATE
WO 2001057277	A2	20010809

DESIGNATED STATES

W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CR CU CZ DE DK DM DZ EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW GH GM KE LS MW MZ SD SL SZ TZ UG ZW AM AZ BY KG KZ MD RU TJ TM AT BE CH CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE TR BF BJ CF CG CI CM GA GN GW ML MR NE SN TD TG

APPLICATION INFO.:	WO 2001-US669	A	20010130
PRIORITY INFO.:	US 2000-60/180,312		20000204
	US 2000-60/207,456		20000526
	US 2000-09/608,408		20000630
	US 2000-09/632,366		20000803
	US 2000-60/234,687		20000921
	US 2000-60/236,359		20000927
	GB 2000-0024263.6		20001004

L21 ANSWER 2 OF 6	PCTFULL COPYRIGHT 2006 Univentio on STN
ACCESSION NUMBER:	2001048227 PCTFULL ED 20020827
TITLE (ENGLISH):	METHOD FOR PRODUCTION OF PROTEINS IN HOST CELLS INVOLVING THE USE OF CHAPERONINS
TITLE (FRENCH):	METHODES DE PRODUCTION DE PROTEINES DANS DES CELLULES HOTES
INVENTOR(S):	JOACHIMIAK, Andrzej;
	DONELLY, Mark
PATENT ASSIGNEE(S):	GENENCOR INTERNATIONAL, INC.
DOCUMENT TYPE:	Patent
PATENT INFORMATION:	

NUMBER	KIND	DATE
WO 2001048227	A1	20010705

DESIGNATED STATES

W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CR CU CZ DE DK DM DZ EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG UZ VN YU ZA ZW GH GM KE LS MW MZ SD SL SZ TZ UG ZW AM AZ BY KG KZ MD RU TJ TM AT BE CH CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE TR BF BJ CF CG CI CM GA GN GW ML MR NE SN TD TG

APPLICATION INFO.:	WO 2000-US34055	A	20001214
PRIORITY INFO.:	US 1999-09/470,830		19991223

L21 ANSWER 3 OF 6	PCTFULL COPYRIGHT 2006 Univentio on STN
ACCESSION NUMBER:	2000071723 PCTFULL ED 20020515
TITLE (ENGLISH):	METHODS FOR REGULATING PROTEIN CONFORMATION USING MOLECULAR CHAPERONES
TITLE (FRENCH):	METHODES DE REGULATION DE LA CONFORMATION DE PROTEINES AU MOYEN DE CHAPERONS MOLECULAIRES
INVENTOR(S):	BUKAU, Bernd;
	GOLOUBINOFF, Pierre
PATENT ASSIGNEE(S):	ROCHE DIAGNOSTICS GMBH;
	BUKAU, Bernd;

GOLOUBINOFF, Pierre
LANGUAGE OF PUBL.: English
DOCUMENT TYPE: Patent
PATENT INFORMATION:

NUMBER	KIND	DATE
WO 2000071723	A2	20001130

DESIGNATED STATES
W: AE AL AM AT AU AZ BA BB BG BR BY CA CH CN CR CU CZ DE DK DM EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW GH GM KE LS MW MZ SD SL SZ TZ UG ZW AM AZ BY KG KZ MD RU TJ TM AT BE CH CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE BF BJ CF CG CI CM GA GN GW ML MR NE SN TD TG
APPLICATION INFO.: WO 2000-EP4501 A 20000518
PRIORITY INFO.: US 1999-60/135,395 19990521
EP 2000-00109270.9 20000428

L21 ANSWER 4 OF 6 PCTFULL COPYRIGHT 2006 Univentio on STN
ACCESSION NUMBER: 2000058352 PCTFULL ED 20020515
TITLE (ENGLISH): BARLEY GENE FOR THIOREDOXIN AND NADP-THIOREDOXIN REDUCTASE
TITLE (FRENCH): GENE D'ORGE POUR REDUCTASE DE THIOREDOXINE ET DE THIOREDOXINE NADP
INVENTOR(S): CHO, Myeong-Je;
DEL VAL, Greg;
CAILLAU, Maxime;
LEMAUX, Peggy, G.;
BUCHANAN, Bob, B.
PATENT ASSIGNEE(S): THE REGENTS OF THE UNIVERSITY OF CALIFORNIA;
CHO, Myeong-Je;
DEL VAL, Greg;
CAILLAU, Maxime;
LEMAUX, Peggy, G.;
BUCHANAN, Bob, B.
LANGUAGE OF PUBL.: English
DOCUMENT TYPE: Patent
PATENT INFORMATION:

NUMBER	KIND	DATE
WO 2000058352	A2	20001005

DESIGNATED STATES
W: AE AG AL AM AT AU AZ BA BB BG BR BY CA CH CN CR CU CZ DE DK DM DZ EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW GH GM KE LS MW SD SL SZ TZ UG ZW AM AZ BY KG KZ MD RU TJ TM AT BE CH CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE BF BJ CF CG CI CM GA GN GW ML MR NE SN TD TG
APPLICATION INFO.: WO 2000-US8566 A 20000331
PRIORITY INFO.: US 1999-60/127,198 19990331
US 1999-60/169,162 19991206
US 2000-60/177,740 20000121
US 2000-60/177,739 20000121

L21 ANSWER 5 OF 6 PCTFULL COPYRIGHT 2006 Univentio on STN
ACCESSION NUMBER: 2000034484 PCTFULL ED 20020515
TITLE (ENGLISH): POLYMORPHIC LOCI THAT DIFFERENTIATE ESCHERICHIA COLI 0157:H7 FROM OTHER STRAINS
TITLE (FRENCH): LOCI POLYMORPHES PERMETTANT DE DISTINGUER ESCHERICHIA COLI 0157:H7 D'AUTRES SOUCHES
INVENTOR(S): TARR, Phillip, I.

```
PATENT ASSIGNEE(S):      CHILDREN'S HOSPITAL AND REGIONAL MEDICAL CENTER;
                         TARR, Phillip, I.
LANGUAGE OF PUBL.:       English
DOCUMENT TYPE:           Patent
PATENT INFORMATION:
                         NUMBER              KIND     DATE
                         --------------------------------
                         WO 2000034484        A1 20000615
DESIGNATED STATES
      W:                 AE AL AM AT AU AZ BA BB BG BR BY CA CH CN CR CU CZ DE
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                         KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX
                         NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA
                         UG US UZ VN YU ZA ZW GH GM KE LS MW SD SL SZ TZ UG ZW
                         AM AZ BY KG KZ MD RU TJ TM AT BE CH CY DE DK ES FI FR
                         GB GR IE IT LU MC NL PT SE BF BJ CF CG CI CM GA GN GW
                         ML MR NE SN TD TG
APPLICATION INFO.:       WO 1999-US29149      A  19991208
PRIORITY INFO.:          US 1998-60/111,493      19981208

L21    ANSWER 6 OF 6      PCTFULL   COPYRIGHT 2006 Univentio on STN
ACCESSION NUMBER:        1999025739 PCTFULL  ED 20020515
TITLE (ENGLISH):         VARIABLE REGION FUSION PEPTIDES THAT FORM EFFECTOR
                         COMPLEXES IN THE PRESENCE OF ANTIGEN
TITLE (FRENCH):          PEPTIDES DE FUSION DE REGION VARIABLE QUI FORMENT DES
                         COMPLEXES EFFECTEURS EN PRESENCE D'ANTIGENES
INVENTOR(S):             MAHONEY, Walt;
                         WINTER, Greg
PATENT ASSIGNEE(S):      BOEHRINGER MANNHEIM CORPORATION;
                         MAHONEY, Walt;
                         WINTER, Greg
LANGUAGE OF PUBL.:       English
DOCUMENT TYPE:           Patent
PATENT INFORMATION:
                         NUMBER              KIND     DATE
                         --------------------------------
                         WO 9925739           A1 19990527
DESIGNATED STATES
      W:                 CA JP US AT BE CH CY DE DK ES FI FR GB GR IE IT LU MC
                         NL PT SE
APPLICATION INFO.:       WO 1998-US20017      A  19980924
PRIORITY INFO.:          US 1997-60/065,719      19971114


=> d kwic 6

L21    ANSWER 6 OF 6      PCTFULL   COPYRIGHT 2006 Univentio on STN
ABEN   The fusion polypeptides of this invention contain a variable region
       sequence linked to an
       effector sequence. The polypeptides do not form stable complexes in
       solution, except in the presence
       of an antigen..  .  .

DETD
       BACKGROUND
         Antibody molecules have been designed by evolution to direct a
       relatively non-specific
       effector function on to a specific target. The antibody
       repertory of an individual can be primed
       against a limitless variety of foreign antigens. Upon revisitation of a
       previously encountered antigen,
       the induced antibody will bind and bring into play elements of
       the complement cascade, or Fc
       receptor bearing cells with all their capabilities.
```

The contemporary biomolecular chemist has capitalized on the targeting specificity of the antibody for diagnostic and therapeutic purposes. Attaching the antibody with a label permits the detection or quantitation of antigen in a test solution. Attaching the antibody to a drug permits targeting to certain cells or tissues. New ways of delivering an effector function by way of an antibody are clearly of benefit.

Immunoassays used in routine clinical measurement involve an antibody specific for an analyte of interest in a biological sample. In separation based assays, the detecting of the complex involves a process wherein the complex formed is physically separated from either unreacted analyte, unreacted antibody, or both (U.S. Patent No. 3,646,346). The complex can be first formed in the fluid phase,. and then subsequently captured by. . . .

(U.S. Patent No. 4,708,929). Two subunits of the enzyme P-galactosidase associate to provide the detectable signal, which is quantitatively affected by analyte-specific antibody except in the presence of a sample containing free analyte.

Recent advances in antibody engineering have produced various artificially engineered antibodies and chimeras. Many of these molecules are superior to the natural antibody in aspects such as stability, size, low production cost, higher affinity, or have additional functions such as bi-specificity.

The isolated heavy and light chain variable domains (VH and VL) of an antibody constitute a heterodimer known as the Fv fragment, which contains a single antigen binding pocket. Fv fragments may dissociate at low protein. . . association between VH and VL did not depend on antigen specificity, and some variable domains associated better with a counterpart from another antibody molecule.

Isolated Fv fragments are expected to have better properties for penetration of solid tumor tissue, lower antigenicity, and improved pharmacokinetics. To prevent dissociation of the VH and VL, a single chain variable region (scFv) can be constructed in which the two variable domains are part of the same polypeptide chain, interconnected by a peptide linker (Tsumoto et al.). A comparison of strategies to stabilize immunoglobulin Fv fragments has been described by Glockshuber et al.

Various other constructs of antibody molecules have been prepared. Monoclonal antibodies of a non-human species can be humanized by placing the three antigen-binding CDR regions of each VH and VL of the specific antibody into the framework of human VH and VL- See, for example, EP 0329400.

Constructs have also been prepared in which antibody binding sites are part of a molecular

chimera. Maeda et al. proposed preparing a chimeric molecule in which an antibody binding monodomain was bioengineered onto Vargula luciferase. Ueda et al. (1992) constructed artificial chimeric cell-surface receptors, combining murine IgM with the cytoplasmic. . . constitutive and independent of antigen binding. With IgM lacking the CH2 domain, autophorphorylation increased with increasing concentrations of hapten-

- 2 -

BSA conjugate. Monovalent hapten could not induce phosphorylation, but inhibited stimulation by the conjugate.

SUMMARY OF THE INVENTION

The fusion polypeptides of this invention contain a variable region sequence linked to an effector sequence. The polypeptides do not form stable complexes in solution, except in the presence of an antigen for which. . .

. . . .

with each other in the presence of an antigen, consisting of a first fusion polypeptide comprising a first variable domain sequence linked to a first effector sequence, and a second fusion polypeptide comprising a second variable domain sequence linked to a second effector sequence, wherein complexing between the first and second variable domain sequences in a solution is stabilized if. . .

. . . .

each other in a solution containing the antigen; c) preparing a first fusion polypeptide in which the first variable domain sequence is linked to the first effector sequence, and a second fusion polypeptide in which the second variable domain sequence is linked to a second effector sequence; and d) confirming that the first fusion polypeptide forms a complex with the second. . .

. . . .

the combined variable region is specific for the model antigen hen egg lysozyme, and the effector sequences are monomer subunits of mitochondrial malate dehydrogenase.

FIG. 7 is a half-tone reproduction of a gel showing the size of the cloned encoding region for mitochondrial malate dehydrogenase.

a covalent linkage between the variable domain sequence and the effector sequence, which can be a peptide bond, a polypeptide linker sequence, or any other type of chemical structure covalently connecting the variable domain and the effector in a manner that permits the. . .

. . . .

which is in the complexed configuration. The two solid lines show VH and VL domains (left and right) of a monoclonal antibody specific for the antigen hen egg lysozyme. In the presence of the antigen, the domains associate along an interface of opposing P-pleated. . .

New York, 1996; and in Chemistry of Protein Conjugation and

Cross-linking by S.S. Wong, CRC Press, 1993.

. . .

with the specificity for a particular antigen is standard practice in the art. General techniques used in raising, purifying and modifying antibodies, and the design and execution of immunoassays, are found in Handbook of Experimental Immunology (D.M.

. . .

Freund's complete adjuvant for the first administration, and Freund's incomplete adjuvant for booster doses. The most common way to produce monoclonal antibodies is to immortalize and clone a splenocyte or other antibody -producing cell recovered from an animal that has been immunized. The cione is immortalized by a procedure such as fusion with a. . .

The treated cells are cloned and cultured, and clones are selected that produce antibody of the desired specificity. Specificity testing is performed on clone supernatants usually by immunoassay.

Other methods for obtaining specific variable regions from antibodies or T cells involve contacting a library of immunocompetent cells or viral particles with the target antigen, and growing out positively selected. . .

. . .

interacting variable regions. The most usual configuration of the fusion peptides is for the C-terminus of each variable region to be linked to the N-terminus of each effector, although other configurations are possible. It is also possible to trim a few residues from the. . .

The opposite approach - that is, adding a linker sequence between the variable sequence and the effector sequence on one or both chains - becomes increasingly more difficult with increasing length of the linker. Precedents for conformational shifts through a connector between neighboring domains certainly exists; however, most notably represented by the immunoglobulins themselves.

Where a linker is necessary, it is appropriate to begin with candidates that form a rigid bridge, such as a sequence predicted to form. . .

. . .

expressing a recombinant polynucleotide encoding it, either by PCR-type amplification or using a suitable expression vector, but polypeptide synthesis or conjugation of separate polypeptides using a cross-linking agent can also be used. The fusion proteins of this invention are designed to be freely soluble in solution, and are. . .

When adapted for use as biopharmaceuticals for human therapy, the variable region sequences, the effector sequences, and the linker sequences (if used) will typically be chosen to recemble human sequences as much as possible, to avoid immunogenicity. The specificity of. . .

. . .

converted into a prodrug according to the strategy outlined in USSN 60/[pending; attorney

docket 33746-3001 1.00]. The strategy involves using a cross-linking agent to form the prodrug into
an inactive loop configuration. The loop contains either a protease recognition sequence in the
amino acid sequence, or else an enzyme cleavable group within the cross-linker. Examples of
0 enzyme cleavable cross-linkers are outlined in USSN 08/883,632, and include those that are
cleavable by glycosidase, phosphatase, amidase or esterase. The combined effector sequences. . . of
the polypeptide pair mediating the prodrug activation would have the corresponding catabolic activity
for either the peptide recognition sequence or the cross-linker
.

. . .
and simplified using the
polypeptide pairs of this invention. In one example, a plastic surface is coated with an antigen-
specific capture antibody, the surface is contacted with the sample, and then the surface is
contacted with the polypeptide pair. Presence of antigen in. . .

. . .
Antigen-dependent association of V, and H
This example describes binding experiments conducted using variable region sequences
from anti-hen egg lysozyme (anti-HEL) monoclonal antibody with the designation HyHEL The Fv
fragment was previously known to form a trimolecular complex of 39 kDa in size, as. . .

. . .
lysine residue (Lys 47) located at the VH. interface mutated to threonine, was made to exclude
possible fragment association. The monoclonal antibody (Mab) with this mutation (VLK49T), which
is analogous to HyHEL-8 VL, retains antigen binding affinity (Lavoie et al.). The mutant VL. . .

. . .
Chem. 69, 28777-28782, 1994)
which encodes pel B signal peptide sequence upstream o the structural genes Of VH and VL of the
antibody HyHEL-10 which is specific to HEL, the 670 bp portion thereof encoding the pelB, VL and
ssi transcription termination sequence were. . .

. . .
mixture was
incubated at 370C for one hour. After further two times of washing, 100 lt I of 1/5000 diluted
peroxidase-labeled anti-MI3 antibody (Pharmacia) in binding buffer was added. The plate was
washed five times after one hour at 370C, and then the sample. . .

Using -the structural-.genes Of VH- and W-dornain of the antibody HyHEL-10 and the vector
plasmid pKTN2, and also using the known procedure, Fv fragments of the HyHEL-1 0 were prepared.

. . .
with a malate dehydrogenase effector
In this example, a pair of fusion polypeptides is obtained that have enzymatic effector
sequences based on mitochondrial malate dehydrogenase.

. . .
sequences,
and X-ray crystallographic data available from the Brookhaven database. The sequences of the

heavy and light chain variable regions of monoclonal antibody HyHEL-1 0 was imposed on the crystal structure of the intact Fv fragment. Various candidate enzymes with homologous or heterologous

- 22. . . .

. . . .

likely to be tested in a standard clinical assay. It is a proven label in other clinical chemistry technologies, and is stable. Mitochondrial malate dehydrogenase is allosterically regulated. Moreover, the

23 -

mechanism of catalysis is understood, which should facilitate adaptation to other substrates where desirable.

. . . .

which is in the complexed configuration. The two solid lines show VH and VL domains (left and right) of the anti-HEL antibody. In the presence of the antigen (hen egg lysozyme), the domains are predicted to associate in the manner shown. The malate. . .

FIG. 7 shows the successful amplification of the mitochondrial malate dehydrogenase (MDH) encoding region from a cDNA library. PCR primers were prepared that hybridize to flanking sequences in the cloning vector. Track 1 (no band): cDNA prepared with cytoplasmic MDH-specific primers, amplified with mitochondrial MDH specific primers. Track 2 (-1 kb band): cDNA prepared with cytoplasmic MDH-specific primers, amplified with cytoplasmic MDH specific primers. Track 3 (no band): cDNA prepared with mitochondrial MDH-specific primers, amplified with cytoplasmic MDH specific primers. Track 4 (-1 kb band): cDNA prepared with mitochondrial MDH-specific primers, amplified with mitochondrial IVIDH specific primers. Tracks 6-8 (no bands): controls. Track 9 (ladder): molecular weight standards.

. . . .

amino acid sequence and nucleic acid sequence of the light chain of HyHEL SEQ. ID NOS:11 and 12 provide the mouse MDH amino acid sequence and nucleic acid sequence. SEQ. ID NOS:13 and 14 provide the pig MDH amino acid sequence and nucleic acid sequence.

MDH variants are designed in which various amino acids at the MDH subunit interface are substituted so as to lessen the dimerization constant. The interface is readily identified from the structure shown in FIG.. . .

. . . .

L 108 of the light chain or His 116 of the heavy chain are attached to the N-terminal of candidate modified MDH sequences. The expressed fusion polypeptides are tested for the criteria of antigen-driven but not substrate-driven association, and the antigen-dependent ability of the. . . of sequence alteration and testing is undertaken as necessary that adjust the amino acids at the effector subunit interface or the linkage between the variable domain sequences and the effector sequences to optimize the properties of the polypeptide pair.

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Borrebaeck, C.A.K. (ed.) W.H.

CLMEN. . . with each other in the presence of an antigen,
consisting of:
a) a first fusion polypeptide comprising a first variable domain
sequence linked to a
first effector sequence;
b) a second fusion polypeptide comprising a second variable domain
sequence linked
to a second effector sequence;
wherein presence of the antigen in a solution containing the fusion
polypeptides
promotes complexing between the first and. . .
. . . .
preceding claim, wherein the first and second effector
sequences are each independently at least about 80% identical to the
monomer subunit of
mitochondrial malate dehydrogenase.
1 5 9. The pair of fusion polypeptides of any of claims 1 to 8, wherein
the first and second. . .
. . . .
each other in a solution containing the antigen;
c) preparing a first fusion polypeptide in which the first variable
domain sequence is
linked to the first effector sequence, and a second fusion
polypeptide in which the second
variable domain sequence is linked to a second effector
sequence; and
d) confirming that the first fusion polypeptide forms a complex with the
second fusion
polypeptide that. . .

=> d kwic 3

L21 ANSWER 3 OF 6 PCTFULL COPYRIGHT 2006 Univentio on STN

DETD . . . acid sequence encoding polypeptide or
protein can be prepared using well known methods. The expression vectors
include a DNA se-
quence operably linked to suitable transcriptional or
translational regulatory nucleotide se-
quences, such as those derived from a mammalian, microbial, viral, or
insect gene.. . . enhancers, an mRNA ri-

bosomal binding site, and appropriate sequences which control transcription and translation initiation and termination. Nucleotide sequences are operably linked when the regulatory sequence functionally relates to the DNA sequence encoding the polypeptide or protein of interest.

For example, a promoter nucleotide sequence is operably linked to a DNA sequence encoding the protein or polypeptide of interest if the promoter nucleotide sequence controls the transcription of the. . .

. . . or a sense oligonucleotide, based upon a cDNA sequence for a given protein is described in, for example, Stein and Cohen, Cancer Res. 48:2659, 1988 and van der Krol et al., BioTechniques 6:958, 1988.

. . . of the polypeptides or proteins of the invention. Antisense or sense oligonucleotides further comprise oligonucleotides having modified sugar-phosphodiester backbones (or other sugar linkages, such as those described in WO91/06629) and wherein such sugar linkages are resistant to endogenous nucleases. Such oligonucleotides with resistant sugar linkages are stable I.n vivo (i. e., capable of resisting enzymatic degradation) but retain sequence specificity to be able to bind to target nucleotide sequences. Other examples of sense or antisense oligonucleotides include those olicronucleotides which are covalently linked to organic moieties, such as those des-'bed in W'O 90/10448, and other moieties that increases affinity of the olicTonucleotide for. . .

Sense or antisense oligonucleotides also may be introduced into a cell containing the target nucleotide sequence by formation of a conjugate with a ligand binding molecule, as described in Alternatively, a sense or an antisense oligonucleotide may be introduced into a. . .

. . . can be treated in accordance with the invention include Creutzfeld-jacob's disease, Alzheimer's disease, Huntington's disease, Ataxia type- 1, cystic fibrosis and cancer. The therapeutically effective dose is preferably delivered with a pharmaceutically acceptable carrier. More preferably, the pharmaceutically acceptable carrier is capable. . .

. . . relationship was investigated by altering the cellular levels of chaperones individually or in combination and analyzing chaperone-substrate interactions by co-immunoprecipitation with chaperone-specific antibodies.

. . . proteins that frequently occurs upon overproduction in bacteria. Furthermore, it was observed that aggregates of thermally denatured proteins (e.g., Malate Dehydrogenase, MDH) show increased staining with Congo red, a widely used marker stain indicative for amyloid fibers.

. . . was conducted to analyze the ability of various chaperones to

disaggregate
I
and refold aggregates of thermosensitive test proteins (including Malate Dehydrogenase (MDH)
Z)
and firef[v luc'ferase). Qualitatively similar results were obtained for all proteins tested, and the
results for MDH are summarized in Figure 6 and Table 3, and described in more detail below.

Incubation of MDH at 47'C caused inactivation and formation of large aggregates, as judged by
loss of its enzymatic activity, an increase in light. . . of aggregates. This is depicted in Figure 6A which shows the
time-dependent inactivation and aggregation (increased turbidity at 550 nm) of mitochondrial
MDH (720 nM) at 47'C without chaperones and in the presence of DTT (10 mM). As shown in
Table 3 and Figure 6A, neither ClpB nor the DnaK system alone, with or without ATP, was active
in disaggregation and refolding of MDH. In contrast, as shown in Table 3 and Ficyure 6B (which
shows the time-dependent disaggregation and reactivation at 25'C of MDH that had been aggre-
gated by heat treatment as described above but supplemented with ClpB, DnaK, DnaJ and GrpE
at concentrations of. . . of, CIpB and the DnaK system allowed complete solubilization within 30 min. and
almost complete reactivation of up to 3 pM MDH within 3-4 hours.

Table 3: Disaaarecration of aggregates of Malate Dehydrogenate (MDH) by chaperones
Time of addition Rate disag Refolding 'elds
Yi
t=O t=45 nN.min.- (20 hrs)
BKJE 47 to 96
B KJE 61 t45 98
KJE B. . . of disaggregation were measured either at tO' (to) or at t45' (t45)- Un-
less indicated otherwise, the concentrations were as follows: MDH.agg, 0.72 PM; CIpB, 0.5 PM,
DnaK, I PM; Dnaj, 0.2 PM, GrpE, 0.1 PM; GroEL, 4 PM; GroES, 4 PM; hptG,. . .

Example 8: Chaperone usage in the treatment of diseases linked to protein malfunction
Chaperones are useful in preventing and reversing the aggregation of proteins linked to
Z) Z)
amyloidoses and prion diseases. Several neuro-degenerative and age related diseases, such as the
Creutzfeld-jakob and Alzheimer diseases are caused bv. . . .

22.4 SynechcystIS#I
100 24.5 12.2 Synechcystis#2
0.8 E. coli
00 H. plyorl
Example I 1: ClpS is established as a co-chaparone of CIpA
Malate dehydrogenase (MDH) (0.9]iM) was aggregated, in the absence of chaperones, by incu-
bation at 47'C for 30 minutes. With reference to Figure 14, following aggregation, MDH activity
was monitored in the absence of chaperones (filled triangle), in the presence of 0.5 [iM CIpS

(filled diamond), 0.5]M CIpA. . . 0.5]tM CIpS (filled circle). As indicated in Figure 14, in the absence of chaperones or the presence of CIpS alone, MDH did not
regain significant activity. In the presence of CIpA alone, up to 30% MDH activity was obtained
after 300 minutes. When CIpA is supplemented with ClpS, both the rate and the yield of MDH
activity was enhanced more than two-fold. Thus, CIpS is established as a potent co-chaperone of
CIpA.

CLMEN. . . The method of claim 25 wherein the disease is Creutzfeld-Jacob's disease, Alzheimer's
disease, Huntington's disease, Ataxia type- 1, cystic fibrosis or cancer.

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Time (min at 47'C)
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Z.ma_ys VLMKVIPGMTVDNAVNIMQEAHVNGLSVVIVCSQSEAEEHCTS..LRG-
Synechc_ystis#1 CLLKYIPGMTGDRAWELTNQVHFDGLAIVWVGPQEQAELYHQ..QLRR'
gynechc_ystis#2 TLIQTVAGMTQPQAVDIMMEAHFNGMSLVITCELEHAEFYCET..LRS
E.coli VLQKFFS.YDVERATQLMLAVHYQGKAICGVFTAEVAETKVAMVNKYA
H.p_Vlori ALRDFFD.KSLEEAKALTSSIHRDGEGVCGVYPYDIARHRAAWVRDKA
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COST IN U.S. DOLLARS                                SINCE FILE      TOTAL
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